

WHAT IS CLAIMED IS:

1. An antibody or antibody fragment thereof that activates an endogenous activity of a human erythropoietin receptor in a mammal but does not interact with a peptide having an amino acid sequence of SEQ ID NO:1.

2. An antibody or antibody fragment thereof that is capable of activating an endogenous activity of a human erythropoietin receptor in a mammal, wherein said antibody or antibody fragment thereof exhibits a binding affinity within one hundred fold of the binding affinity of endogenous human erythropoietin to the erythropoietin receptor.

3. An antibody or antibody fragment thereof that activates an endogenous activity of a human erythropoietin receptor in a mammal, comprising at least one heavy chain variable region having the amino acid sequence of SEQ ID NO: 3 or antibody fragment thereof; wherein said antibody or antibody fragment thereof does not interact with a peptide having an amino acid sequence of SEQ ID NO:1.

4. An antibody or antibody fragment thereof that activates an endogenous activity of a human erythropoietin receptor in a mammal, comprising at least one light chain variable region having the amino acid sequence of SEQ ID NO: 5 or antibody fragment thereof; wherein said antibody or antibody fragment thereof does not interact with a peptide having an amino acid sequence of SEQ ID NO:1.

5. An antibody or antibody fragment thereof that activates an endogenous activity of a human erythropoietin receptor in a mammal, comprising:

at least one heavy chain variable region having the amino acid sequence of SEQ ID NO: 3 or antibody fragment thereof; and

at least one light chain variable region having the amino acid sequence of SEQ ID NO: 5 or antibody fragment thereof,

5 wherein said antibody or antibody fragment thereof does not interact with a peptide having an amino acid sequence of SEQ ID NO:1.

6. An antibody or antibody fragment thereof that activates an endogenous activity of a human erythropoietin receptor in a mammal, comprising

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at least one heavy chain variable region having the amino acid sequence of SEQ ID NO: 7 or antibody fragment thereof; wherein said antibody or antibody fragment thereof does not interact with a peptide having an amino acid sequence of SEQ ID NO:1.

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7. An antibody or antibody fragment thereof that activates an endogenous activity of a human erythropoietin receptor in a mammal, comprising

20 at least one light chain variable region having the amino acid sequence of SEQ ID NO: 9 or antibody fragment thereof; wherein said antibody or antibody fragment thereof does not interact with a peptide having an amino acid sequence of SEQ ID NO:1.

25 8. An antibody or antibody fragment thereof that activates an endogenous activity of a human erythropoietin receptor in a mammal, said antibody comprising:

30 at least one heavy chain variable region having the amino acid sequence of SEQ ID NO: 7 or antibody fragment thereof; and

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at least one light chain variable region having the amino acid sequence of SEQ ID NO: 9 or antibody fragment thereof,

35 wherein said antibody or antibody fragment thereof does not interact with a peptide having an amino acid sequence of

SEQ ID NO:1.

9. An antibody or antibody fragment thereof that activates an endogenous activity of a human erythropoietin receptor in a mammal, comprising

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at least one heavy chain variable region having the amino acid sequence selected from the group consisting of SEQ ID NO: 11, 15, 19, 31, 35, 39, 43, 47, 51 and 55 or antibody fragment thereof, wherein said antibody or antibody fragment thereof does not interact with a peptide having an amino acid sequence of SEQ ID NO:1.

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10. An antibody or antibody fragment thereof that activates an endogenous activity of a human erythropoietin receptor in a mammal, comprising

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at least one light chain variable region having the amino acid sequence of SEQ ID NO: 13, 17, 21, 23, 25, 27, 29, 33, 37, 41, 45, 49, 53 and 57 or antibody fragment thereof, wherein said antibody or antibody fragment thereof does not interact with a peptide having an amino acid sequence of SEQ ID NO:1.

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11. An antibody or antibody fragment thereof that activates an endogenous activity of a human erythropoietin receptor in a mammal, said antibody comprising:

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the amino acid sequences of at least one heavy chain variable region and at least one light chain variable region selected from the group consisting of SEQ ID NO:11/SEQ ID NO:13, SEQ ID NO:15/SEQ ID NO:17, SEQ ID NO:19/SEQ ID NO:21, SEQ ID NO:11/SEQ ID NO:23, SEQ ID NO:11/SEQ ID NO:25, SEQ ID NO:11/SEQ ID NO:27, SEQ ID NO:11/SEQ ID NO:29, SEQ ID NO:31/SEQ ID NO:33, SEQ ID NO:35/SEQ ID NO:37, SEQ ID NO:39/SEQ ID NO:41, SEQ ID NO:43/SEQ ID NO:45, SEQ ID NO:47/SEQ ID NO:49, SEQ ID NO:51/SEQ ID NO:53 and SEQ ID NO:55/SEQ ID NO:57 or antibody fragment thereof, wherein said antibody or antibody fragment thereof does not interact with a peptide having an amino acid sequence of SEQ ID NO:1.

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12. An isolated antibody or antibody fragment thereof capable of binding to a human erythropoietin receptor in a mammal, said antibody comprising:

5 at least one heavy chain variable region having the amino acid sequence of SEQ ID NO: 3 or antibody fragment thereof.

13. An isolated antibody or antibody fragment thereof capable of binding to a human erythropoietin receptor in a mammal, said antibody comprising:

10 at least one light chain variable region having the amino acid sequence of SEQ ID NO: 5 or antibody fragment thereof.

14. An isolated antibody or antibody fragment thereof capable of binding to a human erythropoietin receptor in a mammal, said antibody comprising:

15 at least one heavy chain variable region having the amino acid sequence of SEQ ID NO: 7 or antibody fragment thereof.

15. An isolated antibody or antibody fragment thereof capable of binding to a human erythropoietin receptor in a mammal, said antibody comprising:

20 at least one light chain variable region having the amino acid sequence of SEQ ID NO: 9 or antibody fragment thereof.

25 16. An isolated antibody or antibody fragment thereof capable of binding to a human erythropoietin receptor in a mammal, said antibody comprising:

30 at least one heavy chain variable region having the amino acid sequence of SEQ ID NO: 11 or antibody fragment thereof.

17. An isolated antibody or antibody fragment thereof capable of binding to a human erythropoietin receptor in a mammal, said antibody comprising:

at least one light chain variable region having the amino acid sequence of SEQ ID NO: 13 or antibody fragment thereof.

18. An isolated antibody or antibody fragment thereof capable of binding
5 to a human erythropoietin receptor in a mammal, said antibody comprising:

at least one heavy chain variable region having the amino acid sequence of SEQ ID NO: 15 or antibody fragment thereof.

19. An isolated antibody or antibody fragment thereof capable of binding
10 to a human erythropoietin receptor in a mammal, said antibody comprising:

at least one light chain variable region having the amino acid sequence of SEQ ID NO: 17 or antibody fragment thereof.

20. An isolated antibody or antibody fragment thereof capable of binding
15 to a human erythropoietin receptor in a mammal, said antibody comprising:

at least one heavy chain variable region having the amino acid sequence of
20 SEQ ID NO: 19 or antibody fragment thereof.

21. An isolated antibody or antibody fragment thereof capable of binding
to a human erythropoietin receptor in a mammal, said antibody comprising:

25 at least one light chain variable region having the amino acid sequence of SEQ ID NO: 21 or antibody fragment thereof.

22. An isolated antibody or antibody fragment thereof capable of binding
to a human erythropoietin receptor in a mammal, said antibody comprising:

30 at least one light chain variable region having the amino acid sequence of SEQ ID NO: 23 or antibody fragment thereof.

23. An isolated antibody or antibody fragment thereof capable of binding to a human erythropoietin receptor in a mammal, said antibody comprising:

at least one light chain variable region having the amino acid sequence of SEQ
5 ID NO: 25 or antibody fragment thereof.

24. An isolated antibody or antibody fragment thereof capable of binding to a human erythropoietin receptor in a mammal, said antibody comprising:

10 at least one light chain variable region having the amino acid sequence of SEQ
ID NO:27 or antibody fragment thereof.

25. An isolated antibody or antibody fragment thereof capable of binding to a human erythropoietin receptor in a mammal, said antibody comprising:

15 at least one light chain variable region having the amino acid sequence of SEQ
ID NO:29 or antibody fragment thereof.

26. An isolated antibody or antibody fragment thereof capable of binding
20 to a human erythropoietin receptor in a mammal, said antibody comprising:

at least one heavy chain variable region having the amino acid sequence of
SEQ ID NO:31 or antibody fragment thereof.

25 27. An isolated antibody or antibody fragment thereof capable of binding
to a human erythropoietin receptor in a mammal, said antibody comprising:

at least one light chain variable region having the amino acid sequence of SEQ
ID NO:33 or antibody fragment thereof.

30 28. An isolated antibody or antibody fragment thereof capable of binding
to a human erythropoietin receptor in a mammal, said antibody comprising:

at least one heavy chain variable region having the amino acid sequence of
SEQ ID NO:35 or antibody fragment thereof.

29. An isolated antibody or antibody fragment thereof capable of binding to a human erythropoietin receptor in a mammal, said antibody comprising:

5 at least one light chain variable region having the amino acid sequence of SEQ ID NO: 37 or antibody fragment thereof.

30. An isolated antibody or antibody fragment thereof capable of binding to a human erythropoietin receptor in a mammal, said antibody comprising:

10 at least one heavy chain variable region having the amino acid sequence of SEQ ID NO: 39 or antibody fragment thereof.

31. An isolated antibody or antibody fragment thereof capable of binding to a human erythropoietin receptor in a mammal, said antibody comprising:

15 at least one light chain variable region having the amino acid sequence of SEQ ID NO:41 or antibody fragment thereof.

32. An isolated antibody or antibody fragment thereof capable of binding to a human erythropoietin receptor in a mammal, said antibody comprising:

20 at least one heavy chain variable region having the amino acid sequence of SEQ ID NO: 43 or antibody fragment thereof.

25 33. An isolated antibody or antibody fragment thereof capable of binding to a human erythropoietin receptor in a mammal, said antibody comprising:

30 at least one light chain variable region having the amino acid sequence of SEQ ID NO: 45 or antibody fragment thereof.

34. An isolated antibody or antibody fragment thereof capable of binding to a human erythropoietin receptor in a mammal, said antibody comprising:

at least one heavy chain variable region having the amino acid sequence of SEQ ID NO: 47 or antibody fragment thereof.

5 35. An isolated antibody or antibody fragment thereof capable of binding to a human erythropoietin receptor in a mammal, said antibody comprising:

at least one light chain variable region having the amino acid sequence of SEQ ID NO: 49 or antibody fragment thereof.

10 36. An isolated antibody or antibody fragment thereof capable of binding to a human erythropoietin receptor in a mammal, said antibody comprising:

at least one heavy chain variable region having the amino acid sequence of SEQ ID NO: 51 or antibody fragment thereof.

15 37. An isolated antibody or antibody fragment thereof capable of binding to a human erythropoietin receptor in a mammal, said antibody comprising:

20 at least one light chain variable region having the amino acid sequence of SEQ ID NO: 53 or antibody fragment thereof.

38. An isolated antibody or antibody fragment thereof capable of binding to a human erythropoietin receptor in a mammal, said antibody comprising:

25 at least one heavy chain variable region having the amino acid sequence of SEQ ID NO: 55 or antibody fragment thereof.

30 39. An isolated antibody or antibody fragment thereof capable of binding to a human erythropoietin receptor in a mammal, said antibody comprising:

at least one light chain variable region having the amino acid sequence of SEQ ID NO: 57 or antibody fragment thereof.

40. An isolated antibody capable of binding a human erythropoietin receptor in a mammal, said antibody comprising a heavy chain variable region comprising a continuous sequence from CDR1 through CDR3 having the amino acid sequence selected from the group consisting of: SEQ ID NO:58, SEQ ID NO:59,
5 SEQ ID NO:60, and SEQ ID NO:61 and fragments thereof.

41. An isolated antibody capable of binding a human erythropoietin receptor in a mammal, said antibody comprising a light chain variable region comprising a continuous sequence from CDR1 through CDR3 having the amino acid
10 sequence selected from the group consisting of: SEQ ID NO:62, SEQ ID NO:63, SEQ ID NO:64, SEQ ID NO:65, SEQ ID NO:66, SEQ ID NO:67, SEQ ID NO:68, SEQ ID NO:74, SEQ ID NO:75, SEQ ID NO:76, SEQ ID NO:77, SEQ ID NO:78 and fragments thereof.

15 42. A method of activating an endogenous activity of a human erythropoietin receptor in a mammal, the method comprising the step of administering to said mammal a therapeutically effective amount of an antibody or antibody fragment thereof to activate said receptor, wherein said antibody or antibody fragment thereof does not interact with a peptide having an amino acid sequence of SEQ ID NO:1.

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43. A method of modulating an endogenous activity of a human erythropoietin receptor in a mammal, the method comprising the step of administering to a mammal a therapeutically effective amount of the antibody or antibody fragment of claim 1 to modulate the activity of the receptor.

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44. A method of treating a mammal suffering aplasia, the method comprising the step of administering to a mammal in need of treatment a therapeutically effective amount of an antibody or antibody fragment thereof to activate said receptor, wherein said antibody or antibody fragment thereof does not
30 interact with a peptide having an amino acid sequence of SEQ ID NO:1.

45. A method of treating a mammal suffering aplasia, the method comprising the step of administering to a mammal in need of treatment a

therapeutically effective amount of the antibody or antibody fragment of claim 1 to modulate the activity of the receptor.

5 46. A pharmaceutical composition comprising a therapeutically effective amount of an antibody or antibody fragment thereof and a pharmaceutically acceptable excipient, wherein said antibody or antibody fragment thereof does not interact with a peptide having an amino acid sequence of SEQ ID NO:1.

10 47. An isolated and purified polynucleotide sequence selected from the group consisting of: SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO:10, SEQ ID NO:12, SEQ ID NO:14, SEQ ID NO:16, SEQ ID NO:18, SEQ ID NO:20, SEQ ID NO:22, SEQ ID NO:24, SEQ ID NO:26, SEQ ID NO:28, SEQ ID NO:30, SEQ ID NO:32, SEQ ID NO:34, SEQ ID NO:36, SEQ ID NO:38, SEQ ID NO:40, SEQ ID NO:42, SEQ ID NO:44, SEQ ID NO:46, SEQ ID NO:48, SEQ ID NO:50, SEQ ID NO:52, SEQ ID NO:54, SEQ ID NO:56, fragments, complements, 15 and degenerate codon equivalents thereof.

20 48. An isolated and purified amino acid sequence selected from the group consisting of: SEQ ID NO:3, SEQ ID NO:5, SEQ ID NO:7, SEQ ID NO:9, SEQ ID NO:11, SEQ ID NO:13, SEQ ID NO:15, SEQ ID NO:17, SEQ ID NO:19, SEQ ID NO:21, SEQ ID NO:23, SEQ ID NO:25, SEQ ID NO:27, SEQ ID NO:29, SEQ ID NO:31, SEQ ID NO:33, SEQ ID NO:35, SEQ ID NO:37, SEQ ID NO:39, SEQ ID NO:41, SEQ ID NO:43, SEQ ID NO:45, SEQ ID NO:47, SEQ ID NO:49, SEQ ID NO:51, SEQ ID NO:53, SEQ ID NO:55, SEQ ID NO:57, SEQ ID NO:58, SEQ ID NO:59, SEQ ID NO:60, SEQ ID NO:61, SEQ ID NO:62, SEQ ID NO:63, SEQ ID NO:64, SEQ ID NO:65, SEQ ID NO:66, SEQ ID NO:67, SEQ ID NO:68 and 25 fragments thereof.

30 49. An antibody or antibody fragment thereof that activates an endogenous activity of a human erythropoietin receptor in a mammal wherein said antibody or antibody fragment is a gamma-2 isotype.

50. The antibody or antibody fragment of claim 49 wherein said antibody or antibody fragment is a monoclonal antibody.

51. The antibody or antibody fragment of claim 50 wherein said antibody or antibody fragment is a humanized antibody.

5 52. The antibody or antibody fragment of claim 50 wherein said antibody or antibody fragment is a human antibody.

53. The antibody or antibody fragment of claim 50 wherein said antibody or antibody fragment does not interact with a peptide having an amino acid sequence of
10 SEQ ID NO:1.

54. The antibody or antibody fragment of claim 50 wherein said antibody or antibody fragment is selected from the group consisting of Ab3, Ab12, Ab22, Ab54, Ab60, Ab102, Ab135, Ab145, Ab198, Ab254, Ab267, Ab390, Ab412, Ab430/432,
15 Ab467 and Ab484.

55. A method of activating an endogenous activity of a human erythropoietin receptor in a mammal, the method comprising the step of administering to a mammal a therapeutically effective amount of the antibody or antibody fragment of claim 49 to
20 activate said receptor.

56. A method of modulating an endogenous activity of a human erythropoietin receptor in a mammal, the method comprising the step of administering to a mammal a therapeutically effective amount of the antibody or antibody fragment
25 of claim 49 to modulate the activity of the receptor.

57. A method of treating a mammal suffering aplasia, the method comprising the step of administering to a mammal in need of treatment a therapeutically effective amount of the antibody or antibody fragment of claim 49 to activate the receptor.
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58. A method of treating a mammal suffering aplasia, the method comprising the step of administering to a mammal in need of treatment a therapeutically effective amount of the antibody or antibody fragment of claim 49 to modulate the activity of the receptor.

59. A method of treating a mammal suffering anemia, the method comprising the steps of administering to a mammal in need of treatment a therapeutically effective amount of the antibody or antibody fragment of claim 49 to modulate the activity of the receptor.

60. A pharmaceutical composition comprising a therapeutically effective amount of the antibody or antibody fragment of claim 49 and a pharmaceutically acceptable excipient.

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